Platelet gel in oral and maxillofacial surgery: a single-centre experience

Andrea Dominijanni[1], Maria Giulia Cristofaro[2], Adalgisa Brescia[1], Mario Giudice[2]

[1]Immunohaematology and Transfusion Medicine Unit, "Pugliese Ciaccio" Hospital, Catanzaro; [2]Department of Maxillofacial Surgery, "Magna Graecia" University of Catanzaro, Campus Germaneto, Catanzaro, Italy

Background. Platelet gel is a blood product intended for non-transfusion, therapeutic purposes; it is produced by combining platelet concentrate with cryoprecipitate. Platelet gel stimulates tissue growth and is a key player in tissue regeneration. As an allogeneic product, platelet gel is obtained from the blood of a common type O blood donor, with a platelet count >200x10^3/μL. Most of the beneficial effects of this product are due to the numerous growth factors (PDGF, TGF-β, IGF-1 and IGF-2, EGF, VEGF and FGF) contained in the alpha-granules of platelets. The aim of this study was to confirm that platelet gel is a valuable aid for the surgical repair of alveolar bone loss.

Materials and methods. Our study was carried out on 87 patients with inflammatory or dysembryoplastic osteolytic lesions >2 cm in diameter in jaw bones. For most patients the platelet gel was collected into a 450 mL bag and kept frozen at –40 °C until, whereas for a small group of patients the gel was prepared and activated in the sterile field of the operating theatre.

Results. All of our patients reported a decrease in painful symptoms immediately after surgery. Follow-up showed considerable acceleration of the healing processes in soft tissues and faster bone regeneration.

Conclusion. Multicentre studies are needed in order to standardise the methods for producing platelet gel and the clinical use of this product. Furthermore, for research purposes *in vitro* studies are needed to increase knowledge on the functional network and platelet growth factors and also to investigate the biochemical and molecular mechanisms involved.

Keywords: platelet gel, platelet-rich plasma, PRP, osteolytic lesions, jaws, growth factors.

Introduction

Platelet gel is a blood product intended for non-transfusion therapeutic purposes. It increases and enhances natural haemostasis as well as processes of tissue repair and regeneration. It is produced by combining platelet concentrate (the source of growth factors) with cryoprecipitate (the source of fibrinogen, fibronectin and other procoagulant factors). It stimulates tissues growth and is a key player in tissue regeneration[1-3]. Over the last 20 years, several studies have shown that the growth of tissues in culture increases when platelets are added[4-7].

The blood needed to produce these products can be collected from autologous donors, in those patients who are not candidates for blood bank donation; in all other cases it comes from homologous donation. Platelet-derived growth factors act in synergy with plasma-derived factors to activate a complex network of autocrine functions that modulate healing[8,9]. The properties of platelet gel have been exploited in several medical and surgical specialities, such as orthopaedics[10], dentistry[11,12], vascular and cardiothoracic surgery, geriatrics and dermatology[13-15], and new uses for platelet gel are currently under investigation. A recent study evaluated the effectiveness of platelet gel in the case of myocardial injury. The product was used to promote myocyte remodelling through regeneration, induction of angiogenesis and restoration of the normal composition of the extracellular matrix[16].

The aim of our study was to confirm that platelet gel is a valuable aid for the surgical filling of alveolar bone losses, as has already been reported in the literature.

Materials and methods

In cases of an allogeneic product, platelet gel is obtained from the blood of a common type O donor with a platelet count >200x10^3/μL and negative screening tests. The whole blood is centrifuged at 1700 rpm for 11 min at 22 °C to separate it into red blood cells and platelet-rich plasma. Red blood cells are then infused back into the donor, if the donor's vein has been kept open by injecting a saline solution, or are stored for the planned surgery. The platelet-rich plasma is centrifuged at 3,500 rpm for 11 min at 22 °C to separate the platelet concentrate and platelet-poor plasma. The platelet concentrate is then placed in a mixer, while the platelet-poor plasma is immediately frozen at –80 °C and then stored in a blood bank refrigerator at 4 °C so that it can thaw slowly overnight and produce cryoprecipitate. The next morning the bag containing the thawed platelet-poor plasma is centrifuged (3,000 rpm for 11 min); platelet-poor precipitate and cryoprecipitate are separated and the latter is transferred under sterile conditions into the bag containing the platelet concentrate. The bag containing cryoprecipitate and platelet concentrate is connected in a sterile manner to four 150-mL transfer bags. The 5% of the product left in the connecting tube undergoes bacterial tests, whereas a platelet count is carried out on all the samples: the platelet concentration is usually about 200x10^3/μL. Aliquots are weighed, numbered, registered and stored at a temperature ranging from –30 °C to –80 °C, on average at –40 °C. During the processing phases, several quality controls are carried out: the platelet concentration in the final mix must be greater than 1,000 - 1,500 x10^3/μL, the target fibrinogen concentration in the cryoprecipitate should be greater than 140 mg/unit and the factor VIII concentration should be greater than 70 IU/L. Asepsis of the stored products is also verified and the ratios of growth factors in the aliquots of frozen activated gel are measured.

The mechanisms through which platelet gel has beneficial effects have not yet been completely elucidated. The growth factors abundantly present in platelet alpha-granules, and slowly and steadily released through this gel, are clearly important; however, cytokines and other chemical mediators also play a major role. These intercellular mediators are found normally in the body; under particular circumstances and at high concentrations they have regenerative potential and trigger a chain reaction giving rise to and amplifying a virtuous circle whose ultimate result is healing of the lesion[17-19].

There are several growth factors: those of particular relevance to this study are:

- platelet-derived growth factor (PDGF): this plays a significant role in angiogenesis and mitosis; it also regulates the role played by other growth factors;
- transforming growth factor-beta (TGF-β): this is involved in chemotaxis; it stimulates the activity of fibroblasts and osteoblasts whereas it inhibits osteoclasts;
- insulin-like growth factors 1 and 2 (IGF-1 and IGF-2): these act mainly on osteoblasts;
- epidermal growth factor (EGF): this stimulates epithelial and mesenchymal cells;
- vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF): these two cytokines have key roles in angiogenesis and stimulate endothelial cells.

Our study was carried out on 87 patients in the period spanning from September 2006 to November 2009. Sixteen patients were aged between 12 and 20 years old, while the remaining patients between 21 and 60 years of age. These patients, being cared for in the Department of Maxillofacial Surgery, were selected on the basis of:

- the presence of osteolytic lesions in jaw bones measuring >2 cm in diameter due to symptomatic and/or asymptomatic inflammatory or dysembryoplastic diseases;
- the absence of metabolic or endocrine disorders;
- age, in order to evaluate whether age influences the time for bone regeneration to occur;
- the location of the lesion, patients with lesions in the maxilla and in the mandible were selected to evaluate whether the quality and recovery time also depend on the site of the lesion;
- single or multiple injuries.

In 31 patients the lesion was located in the maxilla (Figures 1, 2, 3, 4, 5, 6, 7 and 8), in 46 patients it was in the mandible (Figures 9, 10, 11, 12 and 13), whereas 10 patients had multiple lesions. All patients underwent surgery to remove the lesions. In the eight cases with multiple lesions autologous platelet gel was used to fill just a residual bone loss, whereas for the remaining lesions no material was adopted. This

choice was taken to evaluate the different biological responses - in terms of bone regeneration - between the areas treated with platelet gel and the other areas. The filling material used for all other patients was simply autologous platelet gel.

From most patients platelet gel was traditionally collected in a 450 mL bag and kept frozen at –40 °C until the surgery; only in a small group of patients was the gel prepared in the operating theatre and activated in a sterile field.

The surgical site was reached through the intra-oral route; the surgical steps involved careful separation of the mucoperiosteal flap by means of osteotomy using well sharpened or rotating instruments. Great care was taken not to damage the periosteum. We were very careful in performing the curettage of the residual cavity surface once the neoplasm had been removed. The cavity was then filled with platelet gel and the mucoperiosteal flap was replaced; in patients over 50 years old, enrichment with bovine collagen was also used because this strengthens tissues regeneration.

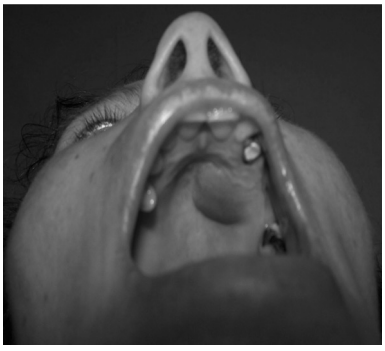

Figure 1 - Views from inside the mouth.

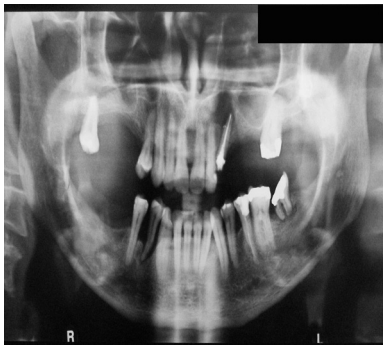

Figure 2 - Maxillary osteolytic lesion on the left side.

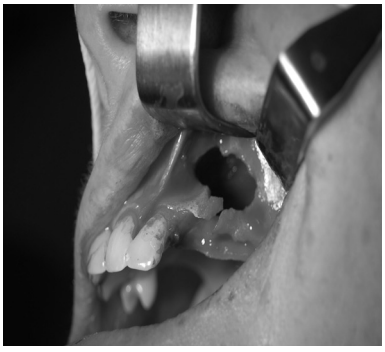

Figure 3 - Intra-operative view.

Figure 4 - Platelet-rich plasma gel.

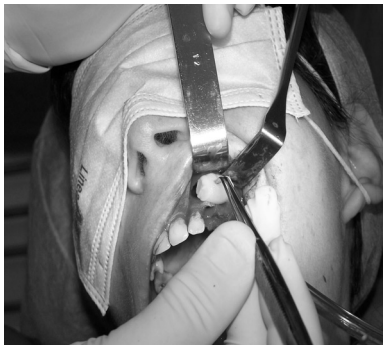

Figure 5 - Cavity filling time with gel.

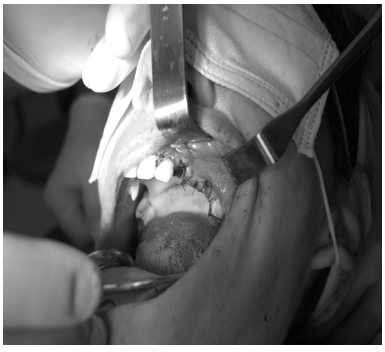

Figure 6 - Flap suture.

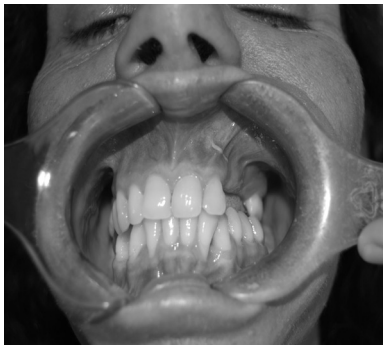

Figure 7 - Follow up 6 months after surgery.

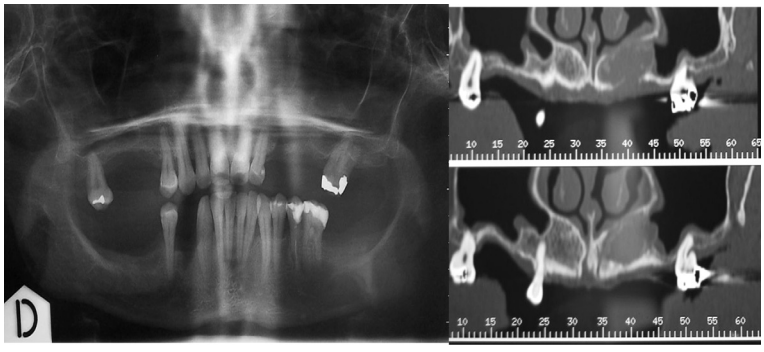

Figure 8 - OPT and CT follow-up, 6 months after surgery.

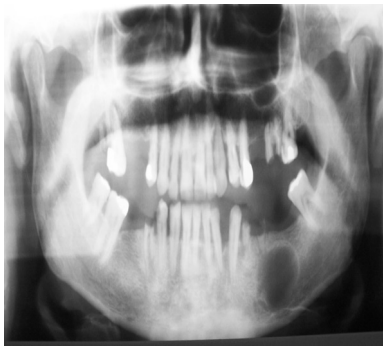

Figure 9 - Osteolytic lesion of the inferior jaw.

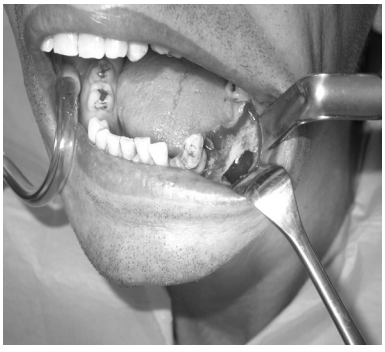

Figure 10 - Intra-operative view.

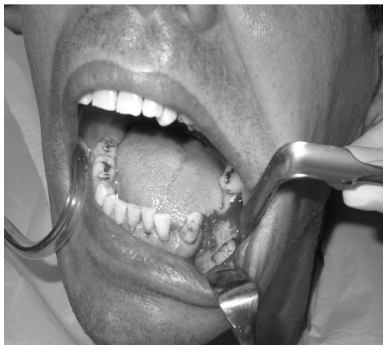

Figure 11 - Cavity filling time with platelet-rich plasma.

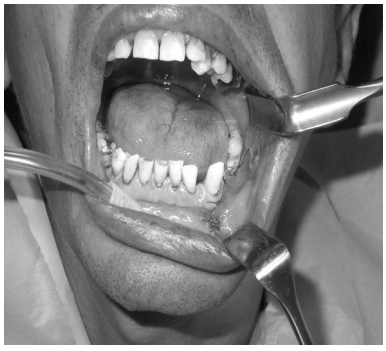

Figure 12 - Flap suture.

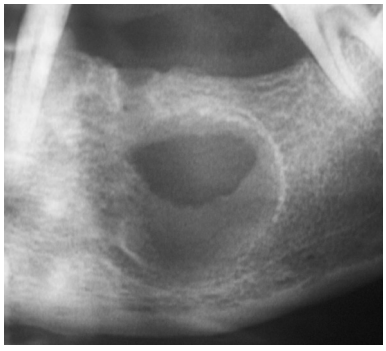

Figure 13 - OPT follow-up 6 months after surgery.

Results

None of the patients had post-operative functional deficits. All of our patients reported a decrease in painful symptoms immediately after surgery. Follow-up consisted of clinical check-ups carried out at 3, 6, 12 and 24 months after surgery and orthopantomography (OPT) and computed tomography (CT) dental scans at 6, 12 and 24 months.

Bone regeneration was slower in the older subset of patients (aged 21 to 60 years old) in whom regeneration took, on average, between 12 and 18 months, while it took only 6 to 12 months for younger patients with injuries of the same size in the same site.

Follow-up assessments showed marked acceleration of healing processes in soft tissues and faster bone regeneration.

Discussion

Platelet gel can be successfully used in several fields and in different medical specialties[20,21]. It is a valuable aid in the following situations, as well as others:

- orthopaedic surgery for the management of pseudo-osteoarthritis with bone loss;
- the treatment of chronic skin ulcers, decubitus or traumatic ulcers as well as diabetic ulcers;
- heart surgery and vascular surgery, for controlling haemostasis;
- ophthalmology, administered as eye drops to treat viral or post-traumatic corneal ulcers.

Its common use in oral and maxillofacial surgery is widely recognised and has been described in the literature over the past years. At our Department we use platelet gel to fill cystic cavities and non-malignant bone deficits.

Small cystic cavities with a diameter <2 cm do not usually need any specific treatment and are not filled with biomaterials. In fact, they are physiologically filled by the blood clot which increases and promotes regenerative processes in human body. However, for cavities with a diameter >2 cm, we envisage the use of biomaterials with osteogenic, osteoinductive and/or osteoconductive properties[22,23].

All this can be avoided by using autologous bone grafts, or autologous filling biomaterials; these latter consist of an inductive tissue (which stimulates migration, proliferation and bone regeneration and increases or enhances the differentiation of local undifferentiated cells into active cells) or a conductive tissue (which holds a structure aiming to regenerate cells and vessels *in situ)*.

Autologous bone is the preferred material, given its biocompatibility and osteogenic and osteoinductive

capacities. However, there are some limitations to its use, including the requirement for particular donor site, physical and mineralogical characteristics which can affect its still unpredictable reabsorption.

Conclusions

Platelet gel is really valuable in the management of alveolar bone loss because of its already reported antiseptic, adhesive and osteoregenerative properties. It is well tolerated and does not cause any harmful side effects. Platelet gel is rich source of growth factors and represents a versatile home-made product. It is less expensive than the one produced in industrial plants and can be prepared *ad personam*, in response to the surgeon's or the patient's needs.

It will be important to perform multicentre studies in the near future in order to standardise the methods of production method and clinical use of platelet gel. *In vitro* studies are required to increase knowledge on the functional network and platelet growth factors as well as to investigate the biochemical and molecular mechanisms involved.

These studies complement the future goal of modern medicine, i.e. the use of stem cells. We hope that both *in vitro* and *in vivo* studies will be carried out in compliance with both the individual's bioethical principles and Hippocrates' ancient medical precept: *"primum non nocere"*.

The Authors declare no conflicts of interest.

References

1) Whitman DH, Berry RL, Green DM. Platelet gel: an autologus alternative to fibrin glue with applications in oral and maxillofacial surgery. J Oral Maxillofac Surg1997; **55**: 1924-9.
2) Matras H. The use of fibrin glue in oral and maxillofacial surgery. J Oral Maxillofac Surg 1982; **40**: 617.
3) Dohan DM, Choukroun J, Diss A, et al. Platelet-rich fibrin (PRF): a second generation platelet concentrate. Part I: technological concepts and evolution. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006; **101**: E37-44.
4) D'Agostino E, Fratellanza G, Caloprisco G, et al. Effetto del gel piastrinico sulla proliferazione cellulare in vitro. La Trasf del Sangue 2002; **47**: 429-33.
5) Weiser L, Bhargava M, Attia E, Torzilli PA. Effect of serum and platelet-derived growth factor on chondrocytes grown in collagen gels. Tissue Eng 1999; **5**: 533-44.
6) Lucarelli E, Beccheroni A, Donati D, et al. Platelet-derived growth factors enhance proliferation of human stromal stem cells. Biomaterials 2003; **24**: 3095-100.
7) Krasna M, Domanoviæ D, Tomsic A, et al. Platelet gel stimulates proliferation of human dermal fibroblasts in vitro. Acta Dermatovenerol Alp Panonica Adriat 2007; **16**: 105-10.
8) Everts PA, Overdest EP, Jakimowicz JJ, et al. The use of autologous platelet-leukocyte gels to enhance the healing process in surgery, a review. Surg Endosc 2007; **21**: 2063-8.
9) Mazzucco L, Medici D, Serra M, et al. The use of autologous platelet gel to treat difficult-to-heal wounds: a pilot study. Transfusion 2004; **44**: 1013-8.
10) Borzini P, Mazzucco L. Tissue regeneration and in loco administration of platelet derivates: outcome, heterogeneous products, and heterogeneity of the effector mechanisms. Transfusion 2005; **45**: 1759-67.
11) Borzini P, Mazzucco L. Platelet gel and releases. Curr Opin Hematol 2005; **12**: 473-9.
12) Rughetti A, Flamini S, Colafarina O, et al. Closed surgery: autologous platelet gel for the treatment of pseudoarthrosis. Blood Transfus 2004; **2**: 37-43.
13) Fontana S, Olmedo ER, Limares JA, et al. Effect of platelet-rich plasma on the peri-implant bone response: an experimental study. Implant Dent 2004; **13**: 73-8.
14) Marx RE, Carlson ER, Eichstaedt RM, et al. Platelet-rich plasma: growth factor enhancement for bone grafts. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998; **85**: 638-46.
15) Borzini P, Mazzucco L, Panizza R, et al. Regarding "Randomized trial and local biological effect of autologous platelets used as adjuvant therapy for chronic venous leg ulcers". J Vasc Surg 2004; **39**: 1146-7.
16) Fecarelli E, Bernuzzi G, Tognetti E, et al. Treatment of chronic venous leg ulcers by platelet gel. Dermatol Ther. 2008; **21**: S13-7.
17) Mogan C, Larson DF. Rationale of platelets gel to augment adaptive remodelling of the injured heart. J Extra Corpor Technol 2004; **36**: 191-6.
18) Cromark DT, Porras-Reyes B, Mustoe TA. Current concepts in wound healing: Growth factor and macrophage interaction. J Trauma 1990; **30**: s130-s132.
19) Pierce GF, VandBerg J, Rudolph R., et al. Platelet-derived growth factor-BB and transforming growth factor beta 1 selectively modulate glycosaminoglycans, collagen, and myofibroblast in excisional wound. Am J Pathol 1991; **138**: 629.
20) Sanchez AR, Sheridan PJ, Kupp LI. Is platelet - rich plasma the perfect enhancement factor? A current review. Int J Oral Maxillofac Implants 2003; **18**: 93-103.
21) Gardner MJ, Demetrakopulos D, Klepchick PR, and Mooar PA. The effacy of autologus platelet gel in pain control and bood loss in total knee arthoplasty. Int Orthop 2007; **31**: 309-13.
22) Meimed EP. Autologus Platelet Gel in Plastic Surgery. Aesthetic Surg J. 2001; **21**: 377-379.
23) Cieslik-Bielecka A, Bielecki T, Gazdzik TS, et al. Improved treatment of mandibular odontogenic cysts with platelet-rich gel. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008; **105**: 423-9.

Arrived: 9 June 2011 - Revision accepted: 8 August 2011
Correspondence: Andrea Dominijanni
Servizio di Immunoematologia e Medicina Trasfusionale
Azienda Ospedaliera Pugliese Ciaccio
Viale Pio X
88100 Catanzaro, Italy
e-mail: domini@unicz.it